DETAILED ACTION

Claims 1, 4-10, 12-17 are pending.

Clarification of the Record/Interview Summary

1. Applicant's Representative, Mr. Richard E. Fichter, Registration No. 26,382 was contacted on June 9, 2009 to clarify the election of species set forth in the response dated March 2, 2009 and to request clarification of claim identifiers submitted with Applicant's response to the election.

2. Mr. Fichter stated that Species A, was and is the elected species (ThyA and CTB containing plasmid); species B (ThyA, CTB and another product ie LTB or a fragment thereof). The examiner stated that the elected species of invention reads on claims 1, 4, 8 ,9, 10, and 12.

3. For clarification of the record, claims 6, 7 (LTB or fragment thereof), claims 5 and 14 which recite SEQ ID NO 1(CTB and LTB fragment (signal peptide) combination), and claims 13, 15-17 all read on species B which is the combination of CTB and a LTB fragment.

4. At which time the elected species defines over the prior art of record, rejoinder of additional species which include/depend from the elected species would be permissible.

5. Claims 1, 4, 8 ,9, 10, and 12 are under consideration.

Information Disclosure Statement

1. The information disclosure statement filed April 28, 2006 has been considered.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Election/Restrictions

3. Applicant's election without traverse of Species A, An expression system for CTB in the reply filed on March 2, 2009 is acknowledged.

4. Claims 5,6-7, 13 (eLTB signal peptide and CTB), 14 and 15-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Species B, that is a combination of CTB together with a heterologous protein (claims 6-7, 15 (CTB and LTB signal peptide, LTB being a heterologous protein), claim 16 directed to a method of protein CTB and LTB signal peptide, and claim 17 directed to a nucleic acid encoding CTB fused to LTB signal peptide coding sequence, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 2, 2009.

5. Claims 1, 4, 8 ,9, 10, and 12 are under consideration.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 4, 8 ,9, 10, and 12 rejected under 35 U.S.C. 103(a) as being unpatentable over Carlin et al (WO99/61634 or US Pat. 7,261,899) in view of Turner et al (WO03/022307, filing date September 11, 2002) .

Carlin et al describe and teach:

Instant claim 1, 4, 10 and 12: an expression system for producing a B subunit of a toxin ("LTB is similar in structure to the B subunit of cholera toxin") the expression system comprises:

(a) a Vibrio cholerae host cell (see WO99' abstract, '899, claims 1)

lacking the functionality of a thyA gene (see '899 claim 1, and WO99' abstract, and pg. 7)

WO99' Page 7

originates from the *V.cholerae* Inaba strain 569B of the classical biotype (ATCC No 25870). The strain has a deletion in the *ctx*A gene [7] and has been made rifampicin resistant [8].

and

lacking a CTA gene (see WO99', page 7, lines 15-17 "The strain has a deletion in the ctxA gene"; '899, col. 5, lines 46-49) and

a plasmid expression vector having a size of 3 kb +/- 20% (see WO99' Fig. 16 "2762 bp)

and

comprising a functional thyA gene from E.coli (see WO99' abstract, E.coli ThyA gene, also see '899, claims 2-5)

WO99' claims

> 2. A *Vibrio cholerae thy* A⁻ strain which is a Δ *thy* A strain lacking the functionality of the *thy* A gene.
>
> 3. A Δ *thy* A strain of *Vibrio cholerae* according to claim 2 comprising one or several episomal autonomously replicating DNA elements having a functional *thy* A gene that enables the strain to grow in the absence of thymine in the growth medium.
>
> 4. A Δ *thy* A strain of *Vibrio cholerae* according to claim 3, wherein the episomal autonomously replicating DNA element is a plasmid.
>
> 5. A Δ *thy* A strain of *Vibrio cholerae* according to claim 3 or 4 comprising a foreign *thy* A gene.
>
> 6. A Δ *thy* A strain of *Vibrio cholerae* according to claim 5, wherein the foreign *thy* A gene is an *E. coli* gene.
>
> 7. A Δ *thy* A strain of *Vibrio cholerae* according to any one of claims 3 to 6, wherein the one or several episomal autonomously replicating DNA elements also comprise a structural gene encoding a homologous or heterologous protein.

and

a toxin beta subunit gene which is substantially free of the flanking sequences immediately contiguous by the 5' and 3' end of the beta subunit gene in the naturally occurring genome of the host cell from which the beta subunit gene is derived (see '899, claim 2, comprises a coding sequence for a toxin "LTB is similar in structure to the B subunit of cholera toxin" ('899, col. 5, lines 34-35).

Instant claims 8-9: Carlin et al describe and teach a method that comprises the steps of:

Transforming a Vibrio cholerae host cell (see'899 col. 10. lines 26-29 (expression vector), col. 10, lines 35-36 "electroported into Vibrio cholerae JS1569ΔThyA" '899, col. 5, lines 45-50 JS1569 is a derivative of parent V. cholerae host cell line 569B (ATCC No. 25870) which is deficient in the CTA gene (also known as ctxA)) and

Culturing the transformed V. cholerae host cell under conditions which permit production of the toxin beta subunit (see'899 col. 10,. Lines 39-44) and

Isolating and/or purifying the toxin beta subunit from the host cell (see '899, col. 10, lines 43-45 "culture medium harvested (isolated)", SDS-PAGE (further purification) and Western blot").

Carlin et al teach the construction of an expression vector without an antibiotic resistance gene/marker that is about 3 kb +/- 20% that comprises an E.coli ThyA gene, and a coding sequence for the beta subunit of a toxin, as well as teaches a method of producing the beta subunit of the toxin by culturing a Vibrio cholera host cell that is lacking a CTA gene and a ThyA gene, teaches that LTB is similar to the structure of the B subunit of cholera toxin but differs from the instantly claimed invention by failing to show the beta subunit coding sequence to be a cholera toxin coding sequence.

Turner et al teach and describe attenuated Vibrio host cells (see title, and page 9, line 24) that express either the coding sequence of the beta subunit of cholera toxin (CT-B) (see page 13, lines 1-4) or beta subunit of E. coli heat labile enterotoxin (LTB) in an analogous art for the purpose of obtaining host cell/expression systems that comprise a plasmid vector of about 3kb, and (see WO03', page 72, claim 42) expressing a product that is highly immunogenic (see WO03', page 13, line 3;see WO03' page 50, line 10 and page 13, lines 3-4)).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the expression system of Carlin et al with the coding sequence of the beta subunit of cholera toxin of Turner et al because Carlin et al teach an about 3 kb plasmid vector that can be used for the expression of a coding sequence without the need for incorporation of antibiotic resistance coding sequences (see Carlin et al WO99', page 1, Background paragraphs), the expression system of Carlin having been used to successfully transform and express the beta subunit of a toxin, LTB, and Turner teaches coding sequences for two beta subunit containing toxins, specifically LTB and CTB, CTB being an obvious alternative for LTB.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a transformed Vibrio cholera host cell as taught by Carlin et al that would express the CT-B coding sequence of Turner because Carlin et al teaches an attenuated Vibrio cholera host cell that was successfully transformed with an expression vector coding for a beta subunit of a toxin which can be transformed with any desired coding sequence to produce the recombinantly expressed product in large quantities (see Carlin WO99', page 2, paragraph 4) and Turner teaches the coding sequence of Carlin et al as well as an additional coding sequence for a second beta subunit of a toxin, specifically CT-B that could be readily incorporated into expression system of Carlin for the attainment of large amounts of the desired beta subunit gene product CTB.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". One of skill in the art would recognize that there is a need art to solve the problem of obtaining large quantities of cholera toxin Beta subunit that can be used to stimulate a strong immune response against a serious human pathogen, without using host cells that comprise antibiotic resistance genes that add to the problem of bacteria becoming increasing resistant to antibiotics. Carlin et al in view of Turner et al provide a solution to this problem, by preparing a product that serves this dual purpose/need in the art of producing CTB in an expression system

that will produce the recombinant product in large quantities without using a host cell that has an antibiotic resistance marker gene introduced into the host cell. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results. Carlin et al in view of Turner obviate the instantly claimed invention as now claimed.

Conclusion

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Various references are being sited to show expression vectors and Vibrio cholera mutant strains. .

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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